Therapeutic vaccination for spinal cord injury: helping the body to cure itself

Ehud Hauben and Michal Schwartz

Department of Neurobiology, The Weizmann Institute of Science, 76100 Rehovot, Israel

Inflammation is thought to exacerbate the outcome of spinal cord injury. However, our findings have led us to view inflammation as a healing response that needs the help of a systemic immune response mediated by T helper 1 (Th1) cells that are specific to the abundant antigens residing in the lesion site. Strains differ in their ability to manifest, at the right time and intensity, a spontaneous T-cell response to antigens at the lesion site and therefore in their ability to generate a local inflammatory response whose outcome is beneficial (maintenance and repair). All strains, however, can benefit from immune intervention that boosts and regulates the inflammatory response. Because recovery comprises multi-step processes, pharmacological intervention will be less effective than well-synchronized, self-healing immune activity. Risk-free neuroprotective intervention might be achieved by post-traumatic vaccination with a weak, non-pathogenic, auto-antigen, causing autoimmune T cells to home to the lesion site where they become activated and therefore activate local phagocytic cells to remove hostile elements and provide growth factors.

Recovery from spinal cord injury (SCI) depends largely on the rescue of spared neurons from subsequent (secondary) degeneration and on the regeneration of damaged axons. Because injury-induced neuronal degeneration causes a major part of the functional loss, SCI can be viewed as a trauma-induced degenerative pathology of the CNS [1]. Small anatomical gains, achieved through either spontaneous or therapeutic neuroprotection, can produce disproportionate functional benefits. For example, $<10\%$ of functional long-tract connections are required for locomotion [2,3].

The function of inflammation after SCI and any other acute or chronic insult to the CNS has long been debated. Concepts such as the immune-privileged status of the CNS and the presence of immune cells in the diseased CNS have fostered the prevailing belief that immune activity in the CNS is detrimental [4]. Many authors consider inflammation to be an important mediator of secondary damage [5–9]. Fitch and his colleagues have demonstrated that inflammatory processes alone can initiate a cascade of secondary tissue damage, progressive cavitation and glial scarring in the CNS, and they suggest that specific molecules that promote inflammation might play a role in initiating secondary neuropathology [10]. This appears to be in line with the observation that recovery in spinally injured rats is promoted by the anti-inflammatory compound methylprednisolone (MP) [11]. In a different experimental paradigm, using a rat strain that is limited in its spontaneous ability to manifest a T-cell-based protective mechanism [12] and known to be susceptible to the development of experimental autoimmune encephalomyelitis (EAE), macrophage depletion had a significant effect on the preservation of myelinated axons but not on the post-traumatic recovery of locomotor activity measured by the BBB (Basso, Beattie and Bresnahan) open-field scale [9]. The authors interpreted these results to mean that macrophages act as effectors of acute secondary degeneration. Lewis rats, however, because of the above-mentioned limitation, represent an exceptional situation [12].

... the role of immune cells in the injured spinal cord does not differ from their role in any other tissue under stress from exogenous (non-self) pathogens.

Other studies indicate that inflammation might beneficially affect the traumatized spinal cord by promoting clearance of cell debris and secretion of neurotrophic factors and cytokines. Immune intervention by macrophages and microglia promotes axonal regeneration [10,13–15]. T-cell-mediated intervention leads to processes of maintenance and repair and promotes functional recovery from CNS trauma [16–18]. A therapeutic cocktail devised by Guth and colleagues, which comprises a combination of anti-inflammatory drugs, including indomethacin, to reduce necrosis caused by prostaglandin synthesis, and pro-inflammatory compounds such as bacterial lipopolysaccharide (LPS) to stimulate the secretory activity of macrophages, improves locomotor function of rats subjected to SCI [19,20]. Along the same lines, it was suggested that animals with limited ability to undergo Wallerian degeneration suffer from limited wound healing and regeneration [21]. Later results showed that treatment with a combination of pro-inflammatory and anti-inflammatory

Corresponding author: Michal Schwartz (michal.schwartz@weizmann.ac.il).

http://tips.trends.com 0165-6147/02/$ - see front matter PII: S0165-6147(02)00013-5

drugs have different manifestations when assessed at an early stage (3 days post-injury) compared with a later stage (21 days post-injury) [22]. Both pro-inflammatory and anti-inflammatory cytokines have been shown to improve the outcome of CNS insults [23–26].

As more pieces are added to the puzzle of post-traumatic CNS inflammation it is increasingly evident that to describe inflammation as a unified event that is 'good' or 'bad' for injured nerves is an oversimplification that presupposes a single (and deleterious) process rather than a phenomenon with diverse manifestations. In our opinion, inflammation is a series of local immune responses that are recruited to cope with the damage inflicted by an insult, and the ultimate outcome of inflammation depends on its regulation (Fig. 1). Accordingly, the conflicting interpretations of inflammation might reflect the common practices of: (1) judging parameters such as the size of injury and cavitation rather than functional recovery; (2) evaluating recovery too soon after the injury; and (3) failing to take due account of the species, the strain and the experimental injury model employed. The beneficial effect of immune activity does not come free of charge. The net effect of inflammation depends on the ratio between the cost and the benefit, which should be judged only at steady state, and only in the damaged CNS. Cells that have therapeutic activity in the injured CNS might, in certain strains, be pathogenic in the healthy CNS. This might also explain the neuronal loss observed after injection of either Zymosan (non-toxic yeast particles that are used to activate macrophages and microglia) into the CNS of healthy rats [10] or encephalitogenic T cells into naive Lewis rats that are susceptible to EAE. Thus, the injection of cells or agents that promote inflammatory conditions in healthy animals might cause some tissue loss. In the traumatized CNS, the same cells and agents might promote recovery [18] and reduce cavitation [27] and, although in some strains or individuals there is a price to pay, the cost is outweighed by the benefit even in those cases in which a transient EAE develops. Our group showed that in Lewis rats with either optic nerve injury (ONI) or SCI, passive transfer of encephalitogenic T cells significantly improves recovery despite transient EAE [18]. If the disease is very severe, however, the cost:benefit ratio might be such that the overall protection is wiped out [28]. Thus, whether inflammation is good or bad for recovery will depend on both the genetic and the local-environment contexts (e.g. timing, intensity and regulation). Table 1 summarizes the potentially beneficial effects reported for the various elements that participate in inflammation in the context of SCI.

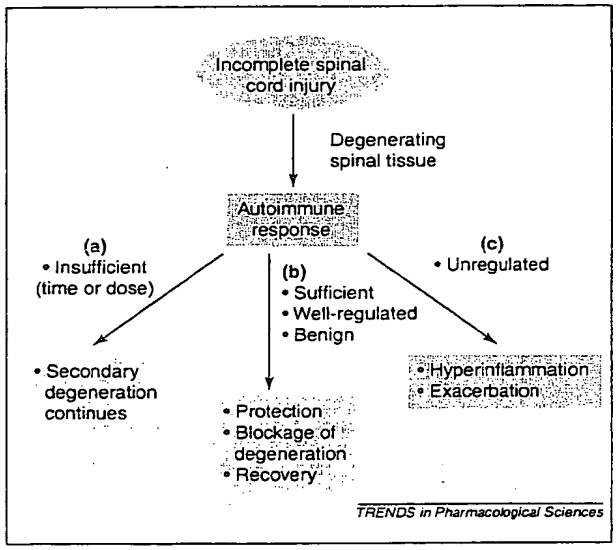

Fig. 1. Incomplete spinal cord injury (ISCI) evokes a physiological autoimmune response to antigens that are associated with the degenerating spinal tissue. (a) Following severe ISCI, the timing and strength of this response is insufficient to completely obstruct the processes of secondary degeneration. (b) Boosting of a controlled response by either passive or active vaccination with myelin antigens, within the therapeutic window for time and dose, can promote a T-cell-mediated protective autoimmune response that can halt the spread of damage and, hence, significantly improve functional recovery. (c) If the response is not controlled it might lead to hyperinflammation and make the functional outcome worse.

Adaptive immunity, in the form of an immune response to self, as a defense mechanism

We have shown that passive transfer of autoimmune T cells into rats with either ONI or SCI results in improved recovery both morphologically and functionally [16,18]. Initially, this unexpected finding was received with skepticism because of the prevailing dogma that: (1) any immune activity in the CNS is detrimental; (2) autoimmunity is destructive; (3) passive transfer of autoimmune T cells is known to cause EAE; and (4) SCI in rats evokes an autoimmune response that in EAE-susceptible rats, after being amplified and transferred to naive syngeneic rats, causes EAE [29]. However, in a strain that is resistant to EAE (Sprague-Dawley), we have found that passive transfer of myelin basic protein (MBP)-stimulated splenocytes from spinally injured rats into freshly injured rats did not induce EAE and significantly improved functional recovery [30].

Further studies confirmed that the cells that cause autoimmune disease and those responsible for neuroprotection are identical and belong to the T helper 1 cell subset [31]. Moreover, the Lewis rat strain in which a post-traumatic autoimmune response was first reported [29], and which led the authors to conclude that SCI evokes a destructive autoimmune response, has limited spontaneous ability to manifest protective autoimmunity [12]. However, from data we obtained subsequently it became apparent that strains of rats and mice that are susceptible to EAE represent a special case [12]. Strains that are relatively resistant to EAE are better able to spontaneously manifest a beneficial, T-cell-dependent response to CNS injury [12,32]. The strain-related difference in post-injury recovery is attributable to the absence of protective mechanisms in susceptible strains rather than the presence of destructive mechanisms [12,32,33]. Differences in the ability to mount a T-cell-based protective response are not only strain dependent but also sex dependent [34]. The observation

Table 1. Reported cellular and molecular immunological events associated with spinal cord neuroprotection and regeneration

Immune factors	Key neuroprotective activities	Refs
T cells	Activation and regulation of inflammation	[17,18,42]
	Secretion of neurotrophins (e.g. BDNF, NGF and NT3)[a] and cytokines (IFN-γ, IL-10 and IL-1β)	[44,45,65]
	Induction of neurotrophin secretion by other cell types	[41]
Macrophages and microglia	Phagocytosis	
	Secretion of neurotrophic factors and cytokines	[41,66]
	Antigen presentation	
	Glutamate uptake	[67]
	Regeneration	[13,14]
Antibodies	Neutralize neurite-growth inhibitors	[58,60]
	Induction of phagocytosis	
Adjuvants	Activation of inflammation	[19]
Cytokines	Activation and regulation of inflammation	[23,25,68]
Dendritic cells	Antigen presentation	[69]
	Activation and regulation of inflammation	

[a]Abbreviations: BDNF, brain-derived neurotrophic factor; IFN-γ, interferon γ; IL-10, interleukin 10; NGF, nerve growth factor; NT3, neurotrophin 3.

that susceptible strains are less able to spontaneously develop a protective, autoimmune T-cell response might be puzzling at first sight. It can be understood, however, in light of the fact that neuroprotective autoimmunity is caused by the ability to spontaneously express autoimmunity at the right time and at the appropriate intensity, as discussed below.

The outcome of well-controlled inflammation is beneficial

Our group has shown recently that after CNS insult, the naturally occurring $CD4^+CD25^+$ regulatory T (TRg) cells suppress the ability to manifest a protective T-cell-mediated response [35,36]. This cell population [37,38] is the same as that discovered years ago and identified as thymus-derived suppressor T cells responsible for maintaining tolerance to self in the periphery [39]. Using transgenic mice that overexpress the T-cell receptor to myelin basic protein (tMBP/Rg +) [30], our group showed that survival of retinal ganglion cells after ONI was better than that of matched wild-type controls. We attributed the better recovery to the abnormally large numbers of autoimmune T cells in the transgenic mice despite the presence of TRg cells. Using similar mice, a worse outcome than in the wild-type controls was reported recently in a model of SCI [40]. This discrepancy might reflect differences in the therapeutic time window and the amount of T cells needed for recovery from ONI and SCI. Results from our laboratory indicate that neuroprotection requires an optimal postoperative ratio of effector: TRg cells, which might vary with the type of lesion and the time after the injury, and is crucial in determining the outcome. Indeed manipulation of regulatory cells dramatically affects the ability of rats and mice to withstand the consequences of a CNS insult [35], which points to the fine balance between beneficial and destructive effects. Moreover, our group has shown that after CNS injury, the spontaneous recovery of wild-type rodents in both resistant and susceptible strains is improved in animals deprived of $CD4^+CD25^+$ TRg cells [35]. These findings rule out the possibility that TRg cells participate in the process of neuroprotection itself, and indicate that their function is related to the ability to maintain autoimmune T cells with a low threshold for activation, without the risk of autoimmune disease [35].

Accumulating data indicate that T helper cells exert their beneficial effect by coordinating the local, innate inflammatory response at the lesion site (Fig. 2). They

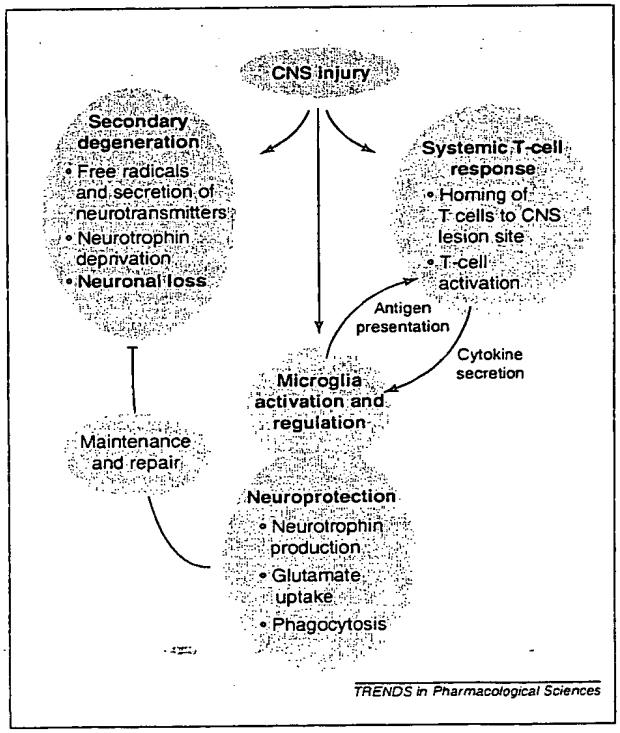

Fig. 2. Cell-mediated immune responses affect the outcome of CNS injury. CNS injury activates both protective and destructive mechanisms. Injury to CNS nerves induces secondary degenerative processes and a systemic T-cell response. T cells home to the injury site, encounter the relevant antigen and are activated. Activated T cells can regulate protective inflammatory processes at the injury site by secreting neurotrophic factors and cytokines that regulate microglial buffering activity. Regulation of both the extent and the timing of the immune response results in less neuronal loss and improved functional outcome.

control the damage by activating resident microglia to: (1) remove dead cells, cell debris and myelin fragments; (2) buffer compounds such as glutamate and nitric oxide that are present in toxic excess of their normal physiological concentrations and toxic; and (3) secrete neurotrophins and cytokines according to the requirements of the injured tissue [27,41–45]. Therefore, the T cells that bring about neuroprotection are those that can be activated at the site of injury by specific antigens presented to them by antigen-presenting cells. In the case of injury to myelinated axons the protective response is evoked by myelin-associated peptides, which are the dominant immunogens at the injury site [18,28,46]. In the case of injury to non-myelinated parts of the CNS, immunodominant antigens that reside at the injury site evoke the protective response [47].

Therapeutic boosting versus therapeutic suppression of inflammation after SCI

Recommendations from the National Acute Spinal Cord Injury Studies include the administration of high doses of intravenous MP as the standard method of treatment for patients with SCI [48]. However, the effect of MP treatment on the outcome of CNS injury is still a matter of controversy [49–52].

If we assume that MP has some beneficial effect at an early stage after the insult, we need to consider how anti-inflammatory and pro-inflammatory treatments can be combined for the patient's benefit. It is possible, as suggested by Zhang *et al.* [22], that different aspects of inflammation are needed at different post-traumatic stages.

In our view, the role of immune cells in the injured spinal cord does not differ from their role in any other tissue under stress from exogenous (non-self) pathogens. A balance is required so that the cost of the immune activity does not exceed the protective benefit [53]. In the absence of proper regulation, activated microglia might either be insufficiently effective or cause deleterious, chronic hyperinflammation. All individuals, even those not inherently equipped with resistance to autoimmune diseases, can benefit from vaccination with myelin peptides [28,31]. In susceptible strains, this beneficial effect might (depending on the choice of antigen used for the vaccination and the adjuvant) come at the price of a transient autoimmune disease [18], accompanied by some loss of neurons [47]. In humans, because of major histocompatibility complex diversity, cryptic (non-pathogenic) epitopes cannot be predicted [53]. Therefore, to design a safe therapeutic strategy for individuals who are susceptible to developing autoimmune diseases in the CNS, it will be necessary to use weak, self-reactive antigens, such as altered-peptide ligands [28]. Our group has discovered that the weak self-reacting antigen Cop-1 (glatiramer acetate) can provide effective neuroprotection in several models of ONI [54,55]. Cop-1, a drug that has been approved by the Food and Drug Administration (FDA) for use in multiple sclerosis, has been proposed as a 'universal antigen' [56]. It is interesting to note that after traumatic injury to myelinated axons, many different, myelin-related antigens, including Nogo, can lead to the same beneficial outcome [28,46].

Rescue of damaged nerves by therapeutic T-cell-mediated vaccination is accompanied by sprouting (O. Butovsky *et al.*, unpublished). Research in the past few years has demonstrated obstacles to sprouting and regeneration in the injured CNS caused by myelin-associated inhibitors of axonal regrowth, scar formation and cavitation [57–60]. Antibodies that neutralize myelin inhibitors facilitate sprouting and regrowth [57]. It was demonstrated that pretrauma immunization with myelin-associated proteins results in regeneration, which was attributed to antibodies [58]. Moreover, passive transfer of Nogo-A-specific antibodies facilitates recovery by a mechanism that leads to efficient myelin clearance [60]. Thus, it seems that recovery can be facilitated not only by autoimmune T cells but also by antibodies to self-antigens. However, the mechanisms that underlie the beneficial effects of these immune factors are still a matter of debate [61,62]. Immune vaccination is one of several ways to augment the local innate response. Another way is by local application of autologous activated macrophages [14]. Both apparently have the effect of helping the local environment to cope with the injurious conditions, allowing better survival of the remaining tissue and cell bodies and the possibility of sprouting and regeneration.

Concluding remarks

The findings outlined above indicate that induction of a well-controlled T-cell-based immune response against self-antigens residing in the lesion site that stimulates protective immunity without risk of triggering an autoimmune disease might be adopted as the basis for a potential therapeutic strategy for the treatment of SCI. Because both degeneration and repair of the damaged spinal cord are highly complex processes that comprise multiple operations, it is unlikely that a single intervention with a single compound (cytokine, neurotrophic factor or drug) will be sufficient. The approach of harnessing the immune system is more likely to supply the multiplicity of factors and processes in the right amounts and at the right time. We suggest that strategies based on T-cell-mediated therapeutic vaccination with a weak self-reactive antigen might be the optimal choice. For clinical application, the choice of the antigen and adjuvant should be based on considerations of safety, such as the risk of autoimmune disease and plasticity in adult CNS [63]. This therapeutic strategy should be viewed not simply as another pharmacological therapy, but as an approach that stimulates the body to use a remedy that has developed through evolution (its own immune system) rather than experimental manipulation [64].

References

1 McDonald, J.W. and Sadowsky, C. (2002) Spinal-cord injury. *Lancet* 359, 417–425
2 Blight, A.R. (1983) Cellular morphology of chronic spinal cord injury in the cat: analysis of myelinated axons by line-sampling. *Neuroscience* 10, 521–543
3 Loy, D.N. *et al.* (2002) Functional redundancy of ventral spinal locomotor pathways. *J. Neurosci.* 22, 315–323
4 Lotan, M. and Schwartz, M. (1994) Cross talk between the immune

system and the nervous system in response to injury: implications for regeneration. *FASEB J.* 8, 1026–1033
5 Carlson, S.L. *et al.* (1998) Acute inflammatory response in spinal cord following impact injury. *Exp. Neurol.* 151, 77–88
6 Dusart, I. and Schwab, M.E. (1994) Secondary cell death and the inflammatory reaction after dorsal hemisection of the rat spinal cord. *Eur. J. Neurosci.* 6, 712–724
7 Mautes, A.E. *et al.* (2000) Vascular events after spinal cord injury: contribution to secondary pathogenesis. *Phys. Ther.* 80, 673–687
8 Ghirnikar, R.S. *et al.* (2001) Chemokine antagonist infusion promotes axonal sparing after spinal cord contusion injury in rat. *J. Neurosci. Res.* 64, 582–589
9 Popovich, P.G. *et al.* (1999) Depletion of hematogenous macrophages promotes partial hindlimb recovery and neuroanatomical repair after experimental spinal cord injury. *Exp. Neurol.* 158, 351–365
10 Fitch, M.T. *et al.* (1999) Cellular and molecular mechanisms of glial scarring and progressive cavitation: *in vivo* and *in vitro* analysis of inflammation-induced secondary injury after CNS trauma. *J. Neurosci.* 19, 8182–8198
11 Constantini, S. and Young, W. (1994) The effects of methylprednisolone and the ganglioside GM1 on acute spinal cord injury in rats. *J. Neurosurg.* 80, 97–111
12 Kipnis, J. *et al.* (2001) Neuronal survival after CNS insult is determined by a genetically encoded autoimmune response. *J. Neurosci.* 21, 4564–4571
13 David, S. *et al.* (1990) Macrophages can modify the nonpermissive nature of the adult mammalian central nervous system. *Neuron* 5, 463–469
14 Rapalino, O. *et al.* (1998) Implantation of stimulated homologous macrophages results in partial recovery of paraplegic rats. *Nat. Med.* 4, 814–821
15 Ousman, S.S. and David, S. (2001) MIP-1α, MCP-1, GM-CSF, and TNF-α control the immune cell response that mediates rapid phagocytosis of myelin from the adult mouse spinal cord. *J. Neurosci.* 21, 4649–4656
16 Moalem, G. *et al.* (1999) Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. *Nat. Med.* 5, 49–55
17 Hauben, E. *et al.* (2000) Autoimmune T cells as potential neuroprotective therapy for spinal cord injury. *Lancet* 355, 286–287
18 Hauben, E. *et al.* (2000) Passive or active immunization with myelin basic protein promotes recovery from spinal cord contusion. *J. Neurosci.* 20, 6421–6430
19 Guth, L. *et al.* (1994) Spinal cord injury in the rat: treatment with bacterial lipopolysaccharide and indomethacin enhances cellular repair and locomotor function. *Exp. Neurol.* 126, 76–87
20 Windle, W.F. (1956) Regeneration of axons in the vertebrae central nervous system. *Physiol. Rev.* 36, 427–440
21 Zhang, Z. *et al.* (1996) Genetic influences on cellular reactions to spinal cord injury: a wound-healing response present in normal mice is impaired in mice carrying a mutation (Wld^s) that causes delayed Wallerian degeneration. *J. Comp. Neurol.* 371, 485–495
22 Zhang, Z. *et al.* (1997) Experimental analysis of progressive necrosis after spinal cord trauma in the rat: etiological role of the inflammatory response. *Exp. Neurol.* 143, 141–152
23 Bethea, J.R. *et al.* (1999) Systemically administered interleukin-10 reduces tumor necrosis factor-α production and significantly improves functional recovery following traumatic spinal cord injury in rats. *J. Neurotrauma* 16, 851–863
24 Kim, G.M. *et al.* (2001) Tumor necrosis factor receptor deletion reduces nuclear factor-κB activation, cellular inhibitor of apoptosis protein 2 expression, and functional recovery after traumatic spinal cord injury. *J. Neurosci.* 21, 6617–6625
25 Mason, J.L. *et al.* (2001) Interleukin-1beta promotes repair of the CNS. *J. Neurosci.* 21, 7046–7052
26 Streit, W.J. *et al.* (2000) Comparative evaluation of cytokine profiles and reactive gliosis supports a critical role for interleukinn-6 in neuron-glia signaling during regeneration. *J. Neurosci. Res.* 61, 10–20
27 Butovsky, O. *et al.* (2001) Morphological aspects of spinal cord autoimmune neuroprotection: colocalization of T cells with B7-2 (CD86) and prevention of cyst formation. *FASEB J.* 15, 1065–1067
28 Hauben, E. *et al.* (2001) Posttraumatic therapeutic vaccination with modified myelin self-antigen prevents complete paralysis while avoiding autoimmune disease. *J. Clin. Invest.* 108, 591–599
29 Popovich, P.G. *et al.* (1996) Concept of autoimmunity following spinal cord injury: possible roles for T lymphocytes in the traumatized central nervous system. *J. Neurosci. Res.* 45, 349–363
30 Yoles, E. *et al.* (2001) Protective autoimmunity is a physiological response to CNS trauma. *J. Neurosci.* 21, 3740–3748
31 Kipnis, J. *et al.* (2002) Myelin specific Th1 cells are necessary for post-traumatic protective autoimmunity. *J. Neuroimmunol.* 130, 78–85
32 Schori, H. *et al.* (2001) T-cell-based immunity counteracts the potential toxicity of glutamate in the central nervous system. *J. Neuroimmunol.* 119, 199–204
33 Serpe, C.J. *et al.* (1999) Exacerbation of facial motoneuron loss after facial nerve transection in severe combined immunodeficient (scid) mice. *J. Neurosci.* 19, RC7
34 Hauben, E. *et al.* (2002) Sexual dimorphisim in the spontaneous recovery from spinal cord injury: a gender gap in beneficial autoimmunity? *Eur. J. Neurosci.* in press
35 Kipnis, J. *et al.* (2002) Neuronal survival after central nervous system injury is improved by depletion of CD4 + CD25 + regulatory T cells and worsened by neonatal tolerance to myelin proteins. *Proc. Natl Acad. Sci. USA* in press
36 Schwartz, M. and Kipnis, J. (2002) Autoimmunity on alert: naturally occurring regulatory CD4 + CD25 + T cells as part of the evolutionary compromise between a 'need' and a 'risk'. *Trends Immunol.* 23, 530–534
37 Seddon, B. and Mason, D. (2000) The third function of the thymus. *Immunol. Today* 21, 95–99
38 Shevach, E.M. *et al.* (2001) Control of T-cell activation by CD4 + CD25 + suppressor T cells. *Immunol. Rev.* 182, 58–67
39 Coutinho, A. *et al.* (1992) Some reasons why deletion and anergy do not satisfactorily account for natural tolerance. *Res. Immunol.* 143, 345–354
40 Jones, T.B. *et al.* (2002) Pathological CNS autoimmune disease triggered by traumatic spinal cord injury: implications for autoimmune vaccine therapy. *J. Neurosci.* 22, 2690–2700
41 Barouch, R. and Schwartz, M. (2002) Autoreactive T cells induce neurotrophin production by immune and neural cells in injured rat optic nerve: Implications for protective autoimmunity. *FASEB J.* 16, 1304–1306
42 Hammarberg, H. *et al.* (2000) Neuroprotection by encephalomyelitis: rescue of mechanically injured neurons and neurotrophin production by CNS-infiltrating T and natural killer cells. *J. Neurosci.* 20, 5283–5291
43 Kerschensteiner, M. *et al.* (1999) Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor *in vitro* and in inflammatory brain lesions: a neuroprotective role of inflammation? *J. Exp. Med.* 189, 865–870
44 Muhallab, S. *et al.* (2002) Differential expression of neurotrophic factors and inflammatory cytokines by myelin basicprotein-specific and other recruited T cells infiltrating the central nervous system during experimentalautoimmune encephalomyelitis. *Scand. J. Immunol.* 55, 264–273
45 Stadelmann, C. *et al.* (2002) BDNF and gp145trkB in multiple sclerosis brain lesions: neuroprotective interactions between immune and neuronal cells? *Brain* 125, 75–85
46 Hauben, E. *et al.* (2001) Vaccination with a Nogo-A-derived peptide after incomplete spinal-cord injury promotes recovery via a T-cell-mediated neuroprotective response: comparison with other myelin antigens. *Proc. Natl Acad. Sci. USA* 98, 15173–15178
47 Mizrahi, T. *et al.* (2002) The tissue-specific self-pathogen is 1 the protective self-antigen: the case of uveitis. *J. Immunol.* 169, 5971–5977
48 Bracken, M.B. *et al.* (1997) Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *J. Am. Med. Assoc.* 277, 1597–1604
49 Hurlbert, R.J. (2000) Methylprednisolone for acute spinal cord injury: an inappropriate standard of care. *J. Neurosurg.* 93, 1–7
50 Qian, T. *et al.* (2000) High-dose methylprednisolone may do more harm for spinal cord injury. *Med. Hypotheses* 55, 452–453

51 Short, D. (2001) Is the role of steroids in acute spinal cord injury now resolved? *Curr. Opin. Neurol.* 14, 759–763
52 Steinsapir, K.D. *et al.* (2000) Methylprednisolone exacerbates axonal loss following optic nerve trauma in rats. *Restor. Neurol. Neurosci.* 17, 157–163
53 Kipnis, J. and Schwartz, M. (2002) Dual action of glatiramer acetate (Cop-1) in the treatment of CNS autoimmune and neurodegenerative disorders. *Trends Mol. Med.* 8, 319–323
54 Kipnis, J. *et al.* (2000) T cell immunity to copolymer 1 confers neuroprotection on the damaged optic nerve: possible therapy for optic neuropathies. *Proc. Natl Acad. Sci. USA* 97, 7446–7451
55 Schori, H. *et al.* (2001) Vaccination for protection of retinal ganglion cells against death from glutamate cytotoxicity and ocular hypertension: implications for glaucoma. *Proc. Natl Acad. Sci. USA* 98, 3398–3403
56 Hafler, D.A. (2002) Degeneracy, as opposed to specificity, in immunotherapy. *J. Clin. Invest.* 109, 581–584
57 Schnell, M. and Schwab, M.E. (1990) Axonal regeneration in the rat spinal cord produced by an antibody against myelin-associated neurite growth inhibitors. *Nature* 343, 269–272
58 Huang, D.W. *et al.* (1999) A therapeutic vaccine approach to stimulate axon regeneration in the adult mammalian spinal cord. *Neuron* 24, 639–647
59 Qiu, J. *et al.* (2002) Spinal axon regeneration induced by elevation of cyclic AMP. *Neuron* 34, 895–903
60 Merkler, D. *et al.* (2001) Locomotor recovery in spinal cord-injured rats treated with an antibody neutralizing the myelin-associated neurite growth inhibitor Nogo-A. *J. Neurosci.* 21, 3665–3673
61 Schwab, M.E. (2002) Repairing the injured spinal cord. *Science* 295, 1029–1031
62 Schwartz, M. and Hauben, E. (2002) Differing views on spinal cord repair. *Science* 296, 1400
63 Raineteau, O. *et al.* (2001) Functional switch between motor tracts in the presence of the mAb IN-1 in the adult rat. *Proc. Natl Acad. Sci. USA* 98, 6929–6934
64 Schwartz, M. and Kipnis, J. (2001) Protective autoimmunity: regulation and prospects for vaccination after brain and spinal cord injuries. *Trends Mol. Med.* 7, 252–258
65 Moalem, G. *et al.* (2000) Production of neurotrophins by activated T cells: implications for neuroprotective autoimmunity. *J. Autoimmun.* 15, 331–345
66 Minghetti, L. and Levi, G. (1998) Microglia as effector cells in brain damage and repair: focus on prostanoids and nitric oxide. *Prog. Neurobiol.* 54, 99–125
67 Nakajima, K. *et al.* (2001) Ability of rat microglia to uptake extracellular glutamate. *Neurosci. Lett.* 307, 171–174
68 Streit, W.J. *et al.* (1998) Cytokine mRNA profiles in contused spinal cord and axotomized facial nucleus suggest a beneficial role for inflammation and gliosis. *Exp. Neurol.* 52, 74–87
69 McTigue, D.M. *et al.* (1998) Selective chemokine mRNA accumulation in the rat spinal cord after contusion injury. *J. Neurosci. Res.* 53, 368–376